

Figure 1

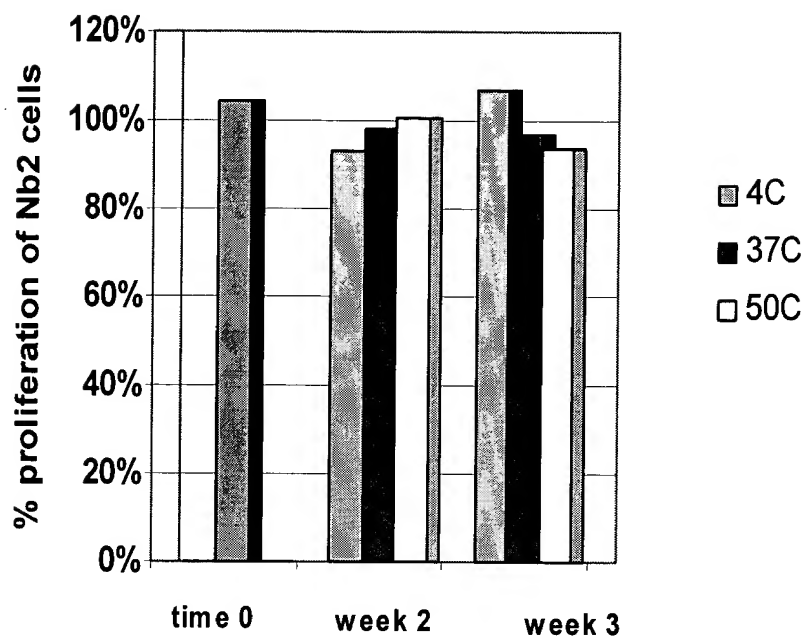


Figure 2

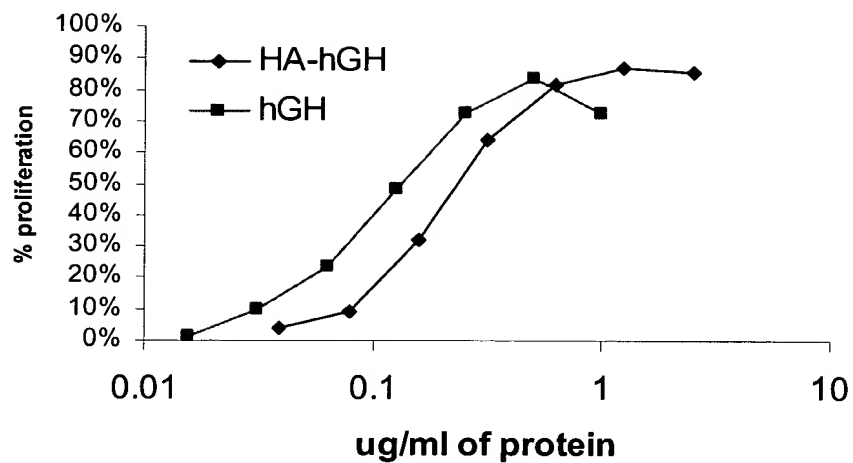


Figure 3A

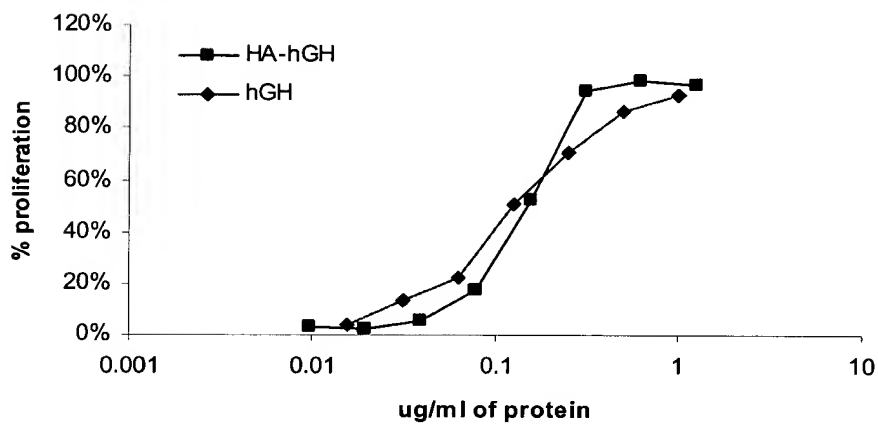


Figure 3B

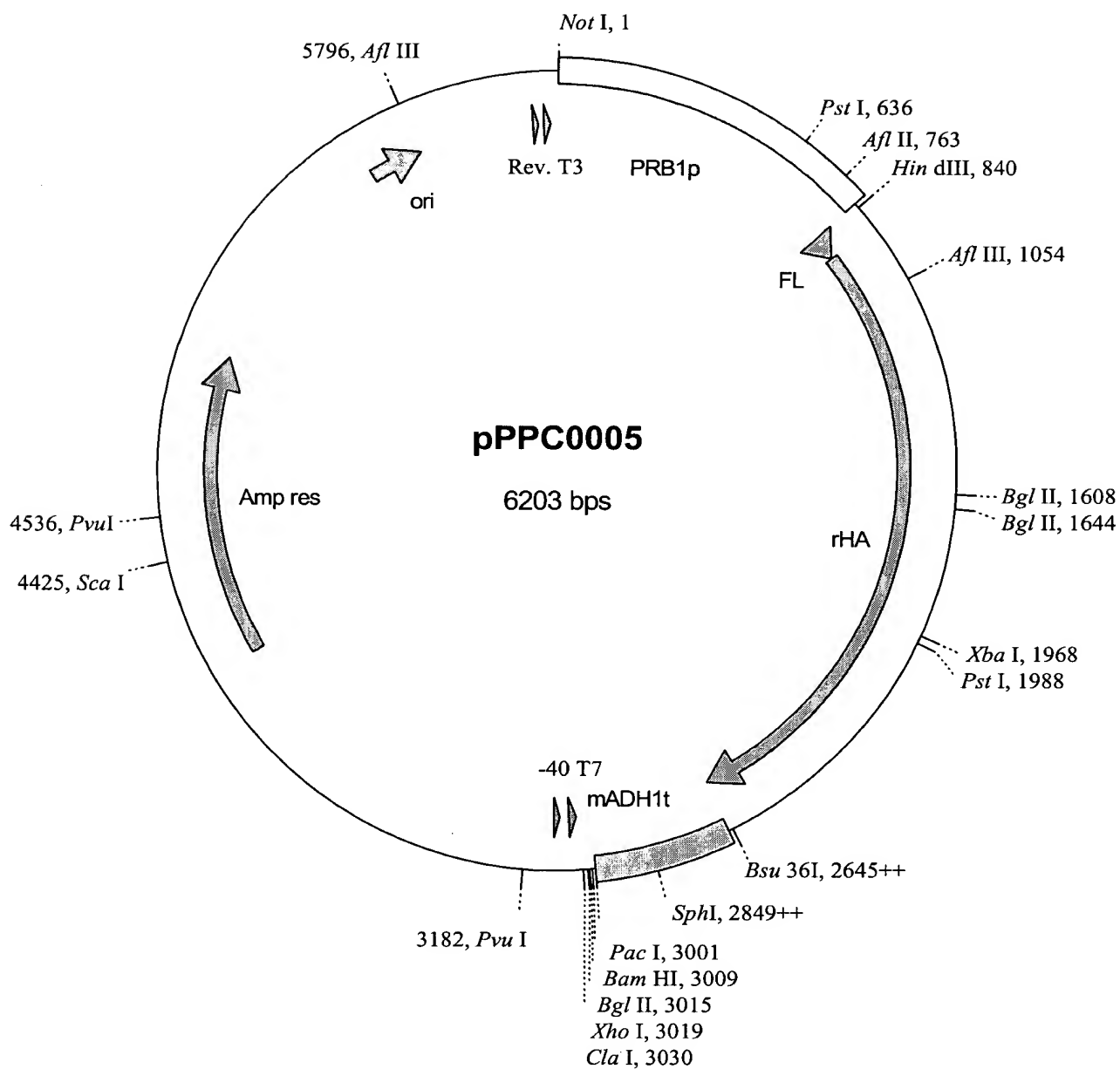


Figure 4

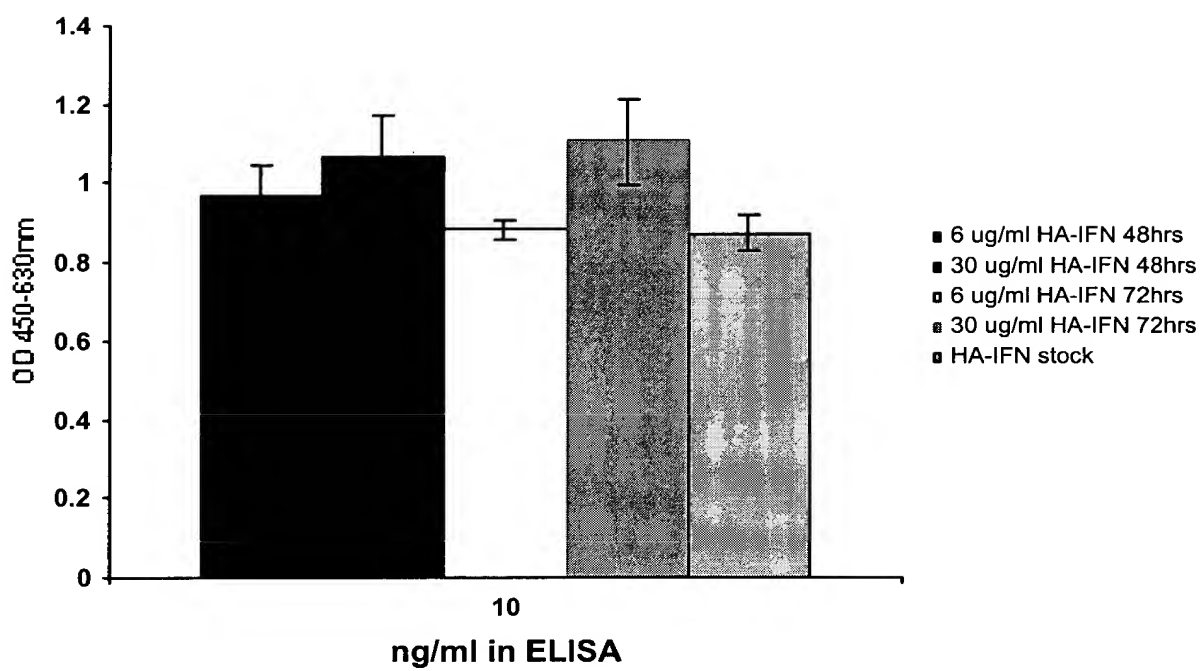
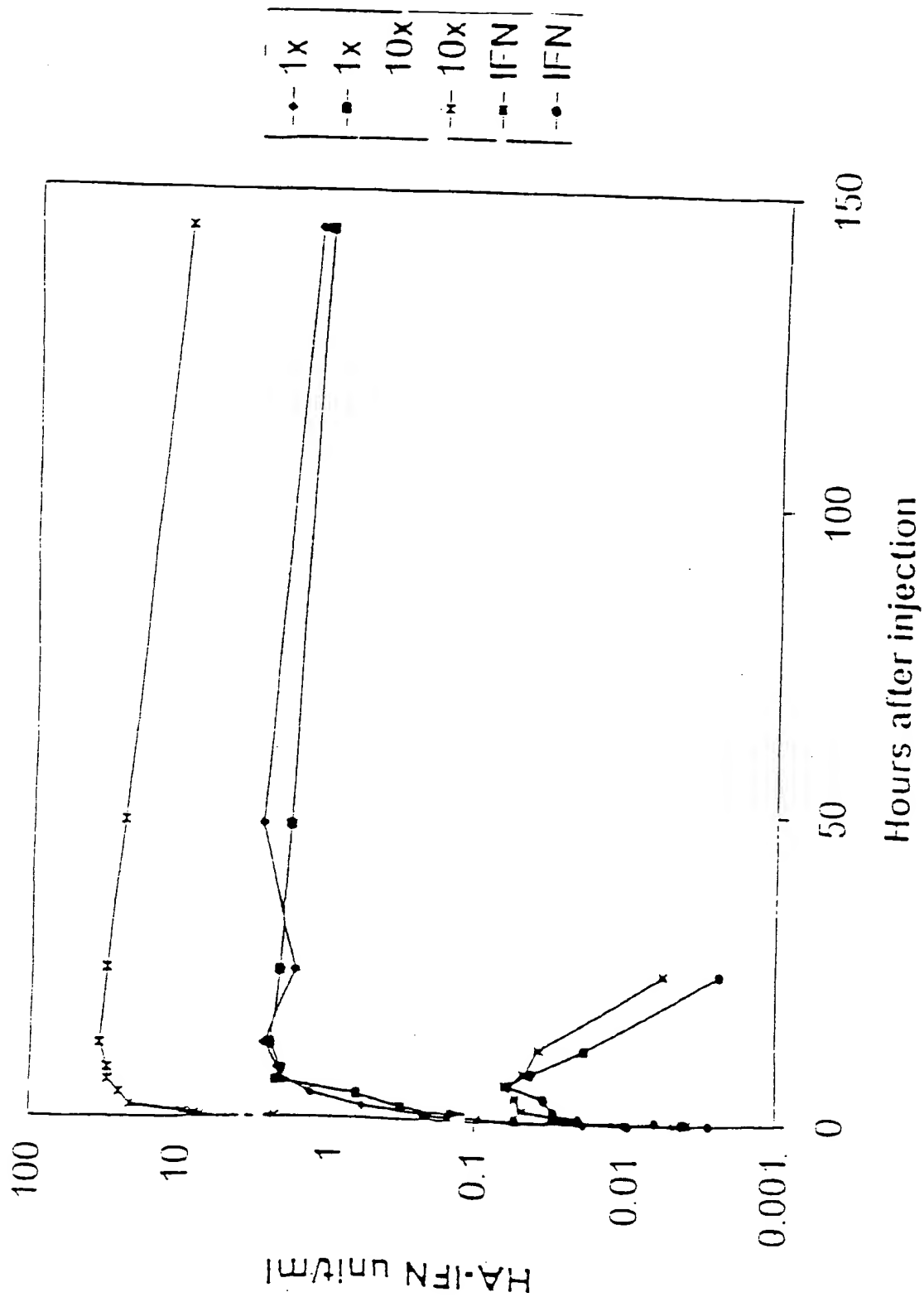


Figure 5

Figure 7



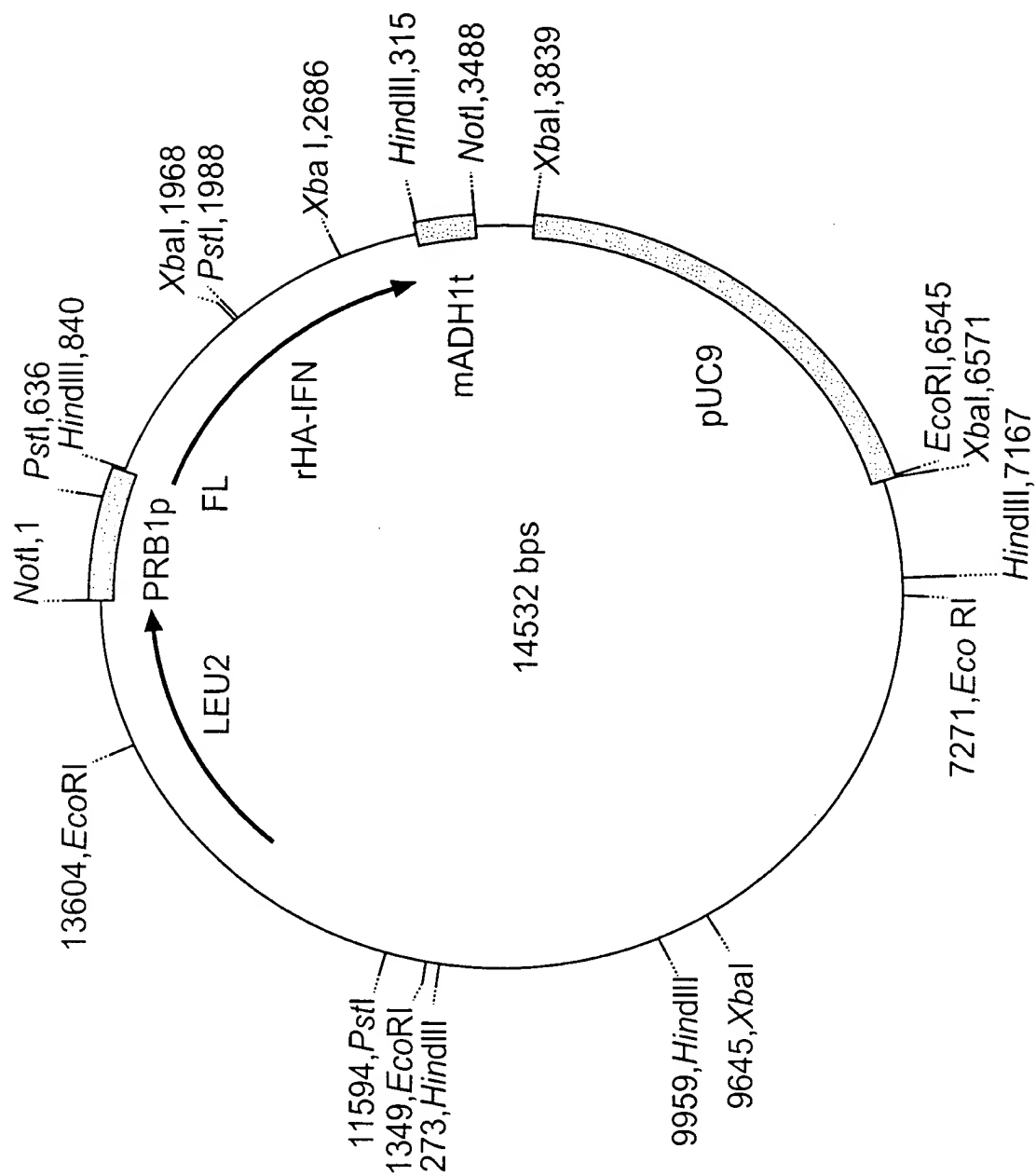


FIG. 8

Figure 9

```

1    DAHKSEVAHR FKDLGEENFK ALVLIAFAQY LQQCPFEDHV KLVNEVTEFA
      HHHHH HHH      HHH HHHHHHHHHHH      HHHHH HHHHHHHHHHH

      I                      II                      III
51   KTCVADESAE NCDKSLHTLF GDKLCTVATL RETYGEMADC CAKOEPERNE
      HHHHH      HHHHH HHHHH      HHHH H      HHHH

101  CFLQHKDDNP NLPRLVRPEV DVMCTAFHDN EETFLKKYLY EIARRHPYFY
      HHHH      H      HHHHHHHHH      HHHHHHHHH HHHHH

      IV
151  APELLFFAKR YKAAFTECCO AADKAACLLP KLDEL RDEGK ASSAKQRLKC
      HHHHHHHHHHH HHHHHHHHH      HHHHH HHHEHHHHHHHH HHHHHHHHHHH

      V
201  ASLQKFGERA FKAWAVARLS QRFPKAEFAE VSKLVTDLTK VHTECCHGDL
      HHHHH      HH HHHHHHHHHHH HH      HHH HHHHHHHHHHH HHHHHH      HH

      VI                      VII
251  LECADDRADL AKYICENODS ISSKLKECCE KPLEKSHCI AEVENDEMPA
      HHHHHHHHHHH HHHHH      HHHHH      HHHHHHH H

301  DLPSLAADFV ESKDVCKNYA EAKDVFLGMF LYEYARRHPD YSVVLLLRLLA
      HHHH      HHHHHH      HHHHHHH HHHHHH      HHHHHHHH

      VIII
351  KTYETTTLEKC CAAADPHECY AKVFDEFKPL VEEPQNLIKQ NCELFEQLGE
      HHHHHHHHHHH      HH      H      HHHHH HHHHHHHHHHH HHHHHHH

      IX
401  YKFQNALLVR YTKKVPQVST PTLVEVSRNL GKVGSKCCKH PEAKRMPCAE
      HHHHHHHHHHH HHHH      H HHHHHHHHHHH      HHH      HHHHHHHH

      X                      XI
451  DYLSVVLNQL CVLHEKTPVS DRVTKCCTES LVNRRPPCFSA LEVDETYVPK
      HHHHHHHHHHH HHHHH      HHHHHHHHHH      HHHHHHHHH

501  EFNAETFTFH ADICTLSEKE RQIKKQTALV ELVKHKPKAT KEQLKAVMDD
      HHH      HHH HHHHMMEHHS HHH      HHHHHHHH

      XII
551  FAAFVEKCCK ADDKETCFAE EGKKLVAAASQ AALGL
      HHHHHHHH      HHHH HHHHHHHHHHH HH
  
```

Loop

I Val54-Asn61
 II Thr76-Asp89
 III Ala92-Glu100
 IV Gln170-Ala176
 V His247-Glu252
 VI Glu266-Glu277

Loop

VII Glu280-His288
 VIII Ala362-Glu368
 IX Lys439-Pro447
 X Val462-Lys475
 XI Thr478-Pro486
 XII Lys560-Thr566

Figure 10

a. Randomisation of Loop IV.

151 APELLFFAKR YKAAFTECCQ ^{IV}AADKAACLLP KLDEL RDEGK ASSAKQRLKC
 HHHHHHHHHH HHHHHHHHHH HHHHH HHHHHHHHHHH HHHHHHHHHHH

151 APELLFFAKR YKAAFTECCX ^{IV}XXXXXXCLLP KLDEL RDEGK ASSAKQRLKC
 HHHHHHHHHH HHHHHHHHHH HHHHH HHHHHHHHHHH HHHHHHHHHHH

X represents the mutation of the natural amino acid to any other amino acid. One, more or all of the amino acids can be changed in this manner. This figure indicates all the residues have been changed.

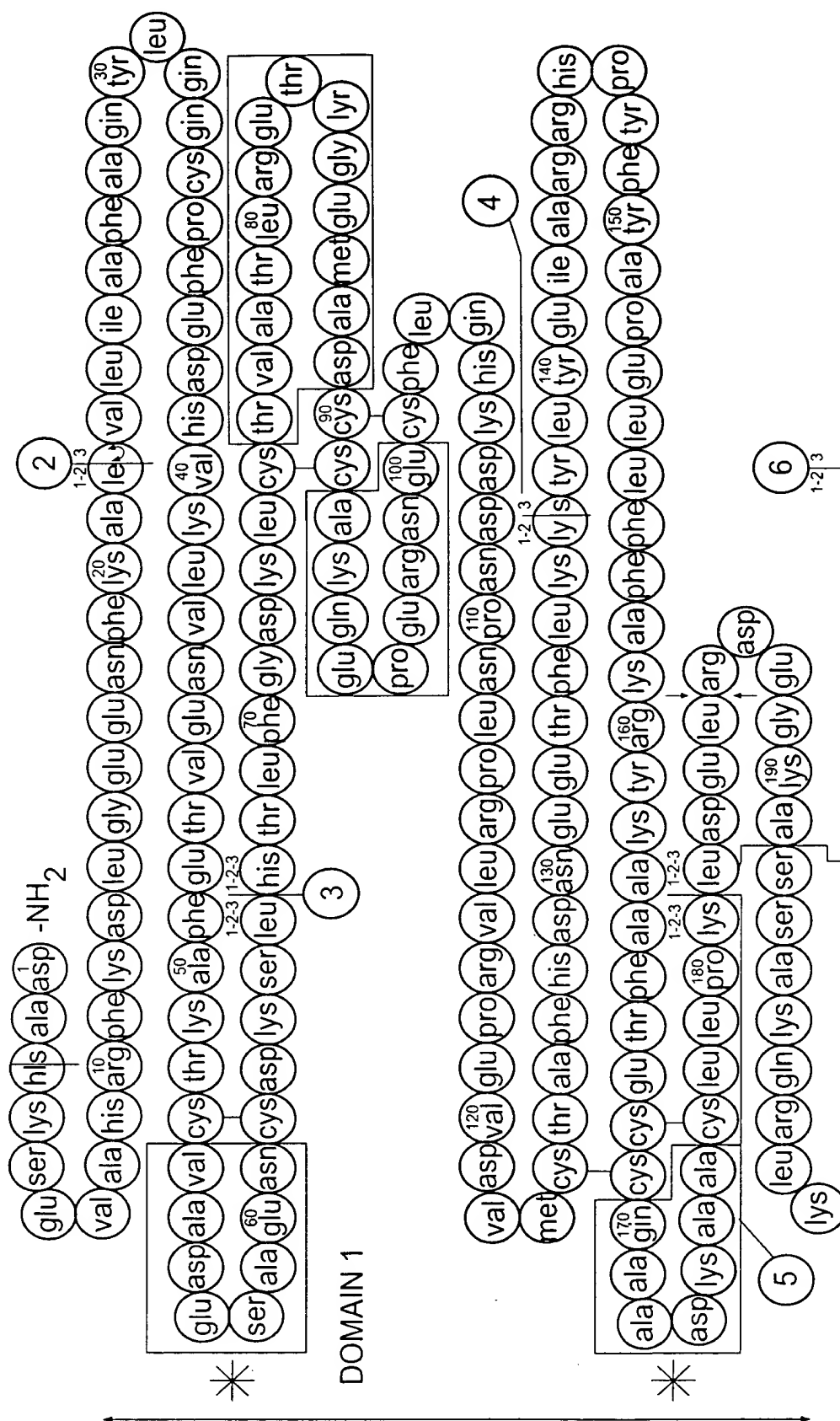
b. Insertion (or replacement) of Randomised sequence into Loop IV.

(X)_n



151 APELLFFAKR YKAAFTECCQ ^{IV}AADKAACLLP KLDEL RDEGK ASSAKQRLKC
 HHHHHHHHHH HHHHHHHHHH HHHHH HHHHHHHHHHH HHHHHHHHHHH

The insertion can be at any point on the loop and a length where n would typically be 6, 8, 12, 20 or 25.



TO FIG. 11B

TO FIG. 11B

FIG. 11A

FIG. 11B

FROM FIG. 11B

FROM FIG. 11B

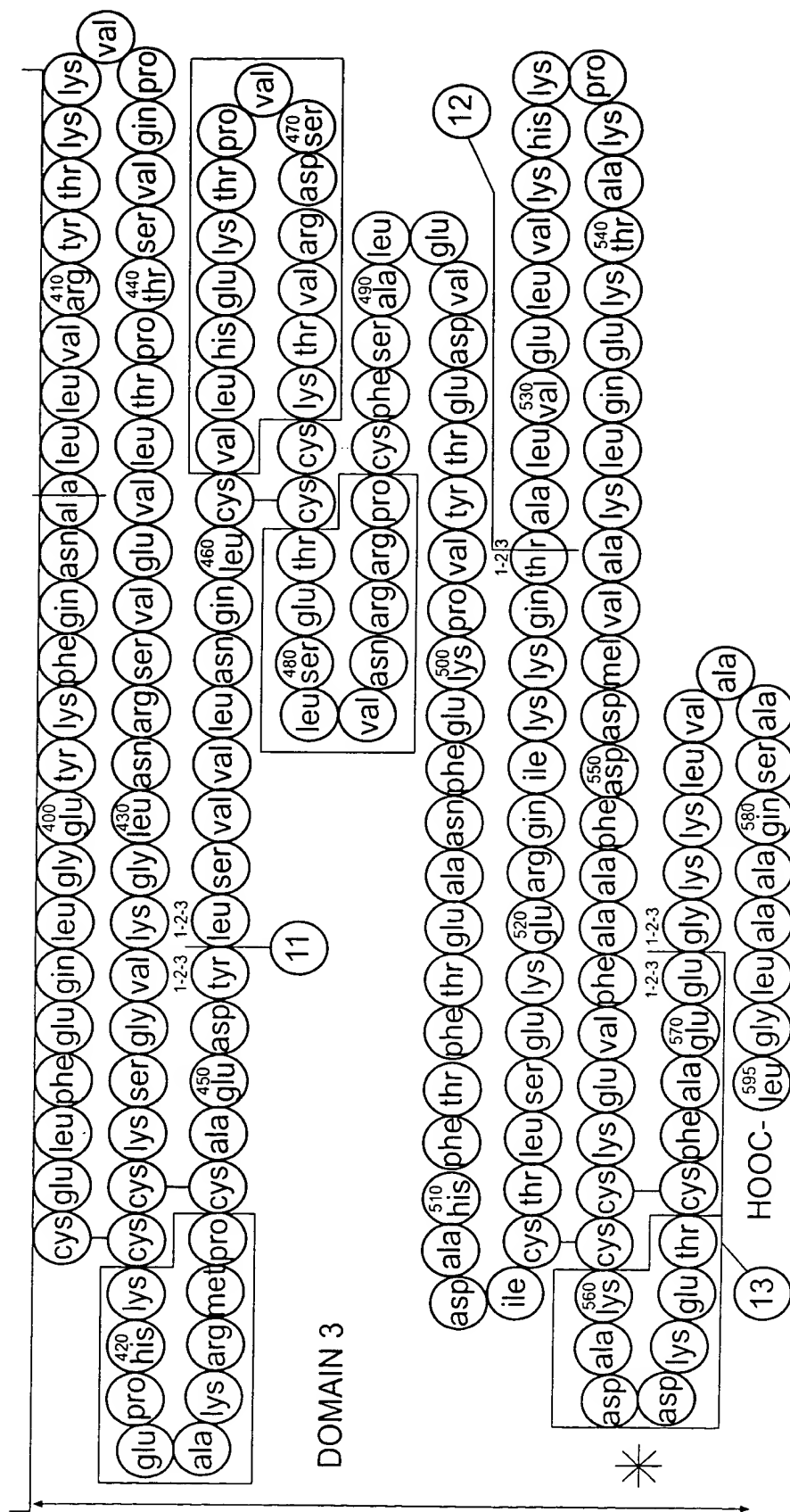


FIG. 11C

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100

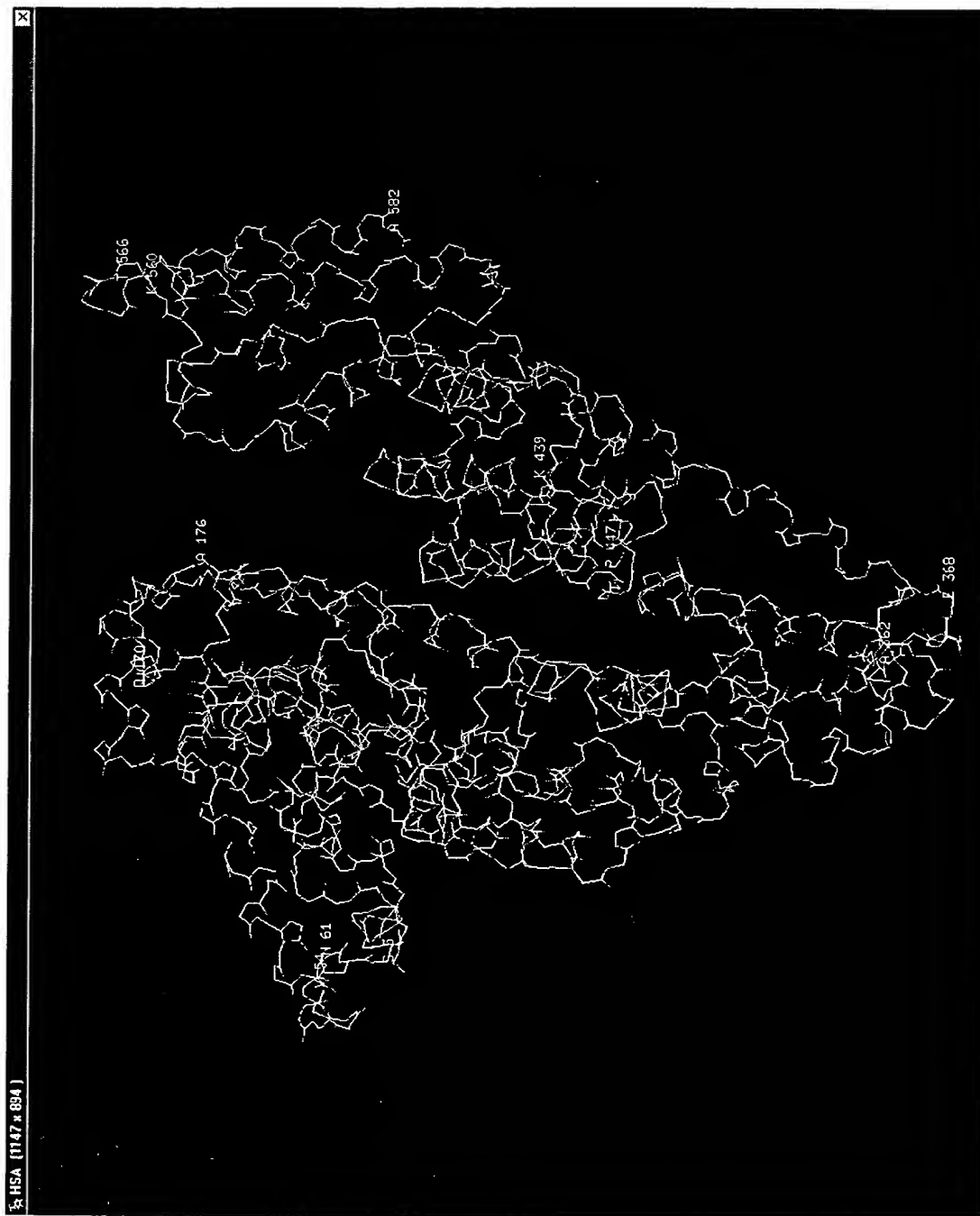


FIG. 13
TERTIARY STRUCTURE OF HA

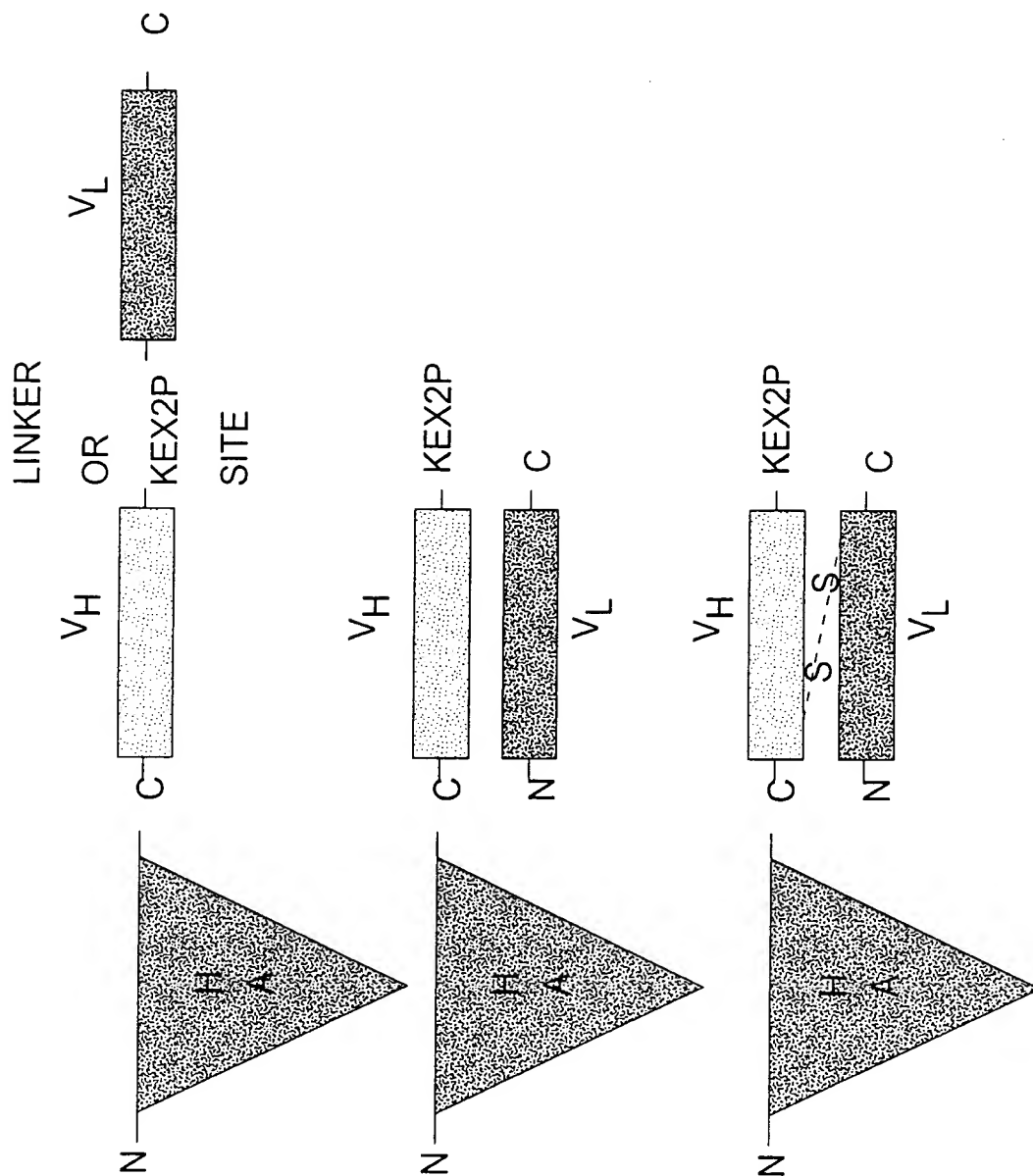


FIG. 14

1 GAT GCA CAC AAG AGT GAG GTT GCT CAT CGG TTT AAA GAT TTG GGA GAA AAT TTC AAA 60
 1 D A H K S E V A H R F K D L G E E N F K 20
 61 GCC TTG GTG ATT GCC TTT GCT CAG TAT CTT CAG CAG TGT CCA TTT GAA GAT CAT GTA 120
 21 A L V L I A F A Q Y L Q Q C P F E D H V 40
 121 AAA TTA GTG AAT GAA GTA ACT GAA TTT GCA AAA ACA TGT GTT GCT GAT GAG TCA GCT GAA 180
 41 K L V N E V T E F A K T C V A D E S A E 60
 181 AAT TGT GAC AAA TCA CTT CAT ACC CTT TTT GGA GAC AAA TTA TGC ACA GTT GCA ACT CTT 240
 61 N C D K S L H T L F G D K L C T V A T L 80
 241 CGT GAA ACC TAT GGT GAA ATG GCT GAC TGC TGT GCA AAA CAA GAA CCT GAG AGA AAT GAA 300
 81 R E T Y G E M A D C C A K Q E P E R N E 100
 301 TGC TTC TTG CAA CAC AAA GAT GAC AAC CCA AAC CTC CCC CGA TTG GTG AGA CCA GAG GTT 360
 101 C F L Q H K D N P N L P R L V R P E V 120
 361 GAT GTG ATG TGC ACT GCT TTT CAT GAC AAT GAA GAG ACA TTT TTG AAA AAA TAC TTA TAT 420
 121 D V M C T A F H D N E E T F L K K Y L Y 140
 421 GAA ATT GCC AGA AGA CAT CCT TAC TTT TAT GCC CCG GAA CTC CTT TTC TTT GCT AAA AGG 480
 141 E I A R R H P Y F Y A P E L L F F A K R 160

Figure 15A

481	TAT	AAA	GCT	GCT	TTT	ACA	GAA	TGT	TGC	CAA	GCT	GCT	GAT	AAA	GCT	GCC	TGC	CTG	TTG	CCA	540
161	Y	K	A	A	F	T	E	C	C	Q	A	A	D	K	A	A	C	L	L	P	180
541	AAG	CTC	GAT	GAA	CTT	CGG	GAT	GAA	GGG	AAG	GCT	TGC	TCT	GCC	AAA	CAG	AGA	CTC	AAA	TGT	600
181	K	L	D	E	L	R	D	E	G	K	A	S	S	A	K	Q	R	L	K	C	200
601	GCC	AGT	CTC	CAA	AAA	TTT	GGA	GAA	AGA	GCT	TTC	AAA	GCA	TGG	GCA	GTG	GCT	CGC	CTG	AGC	660
201	A	S	L	Q	K	F	G	E	R	A	F	K	A	W	A	V	A	R	L	S	220
661	CAG	AGA	TTT	CCC	AAA	GCT	GAG	TTT	GCA	GAA	GTT	TCC	AAG	TTA	GTG	ACA	GAT	CTT	ACC	AAA	720
221	Q	R	F	P	K	A	E	F	A	E	V	S	K	L	V	T	D	L	T	K	240
721	GTC	CAC	ACG	GAA	TGC	TGC	CAT	GGA	GAT	CTG	CTT	GAA	TGT	GCT	GAT	GAC	AGG	GCG	GAC	CTT	780
241	V	H	T	E	C	C	H	G	D	L	L	E	C	A	D	D	R	A	D	L	260
781	GCC	AAG	TAT	ATC	TGT	GAA	AAT	CAG	GAT	TCG	ATC	TCC	AGT	AAA	CTG	AAG	GAA	TGC	TGT	GAA	840
261	A	K	Y	I	C	E	N	Q	D	S	I	S	S	K	L	K	E	C	C	E	280
841	AAA	CCT	CTG	TTG	GAA	AAA	TCC	CAC	TGC	ATT	GCC	GAA	GTG	GAA	AAT	GAT	GAG	ATG	CCT	GCT	900
281	K	P	L	L	E	K	S	H	C	I	A	E	V	E	N	D	E	M	P	A	300
901	GAC	TTG	CCT	TCA	TTA	GCT	GCT	GAT	TTT	GTT	GAA	AGT	AAG	GAT	GTT	TGC	AAA	AAC	TAT	GCT	960
301	D	L	P	S	L	A	A	D	F	V	E	S	K	D	V	C	K	N	Y	A	320

Figure 15B

961	GAG	GCA	AAG	GAT	GTC	TTC	CTG	GGC	ATG	TTT	TTG	TAT	GAA	TAT	GCA	AGA	AGG	CAT	CCT	GAT	1020
321	E	A	K	D	V	F	L	G	M	F	L	Y	E	Y	A	R	R	H	P	D	340
1021	TAC	TCT	GTC	GTG	CTG	CTG	CTG	AGA	CTT	GCC	AAG	ACA	TAT	GAA	ACC	ACT	CTA	GAG	AAG	TGC	1080
341	Y	S	V	V	L	L	L	R	L	A	K	T	Y	E	T	T	L	E	K	C	360
1081	TGT	GCC	GCT	GCA	GAT	CCT	CAT	GAA	TGC	TAT	GCC	AAA	GTG	TTC	GAT	GAA	TTT	AAA	CCT	CTT	1140
361	C	A	A	A	D	P	H	E	C	Y	A	K	V	F	D	E	F	K	P	L	380
1141	GTG	GAA	GAG	CCT	CAG	AAT	TTA	ATC	AAA	CAA	AAC	TGT	GAG	CTT	TTT	GAG	CAG	CTT	GGA	GAG	1200
381	V	E	E	P	Q	N	L	I	K	Q	N	C	E	L	F	E	Q	L	G	E	400
1201	TAC	AAA	TTC	CAG	AAT	GCG	CTA	TTA	GTT	CGT	TAC	ACC	AAG	AAA	GTA	CCC	CAA	GTG	TCA	ACT	1260
401	Y	K	F	Q	N	A	L	L	V	R	Y	T	K	K	V	P	Q	V	S	T	420
1261	CCA	ACT	CTT	GTA	GAG	GTC	TCA	AGA	AAC	CTA	GGA	AAA	GTG	GGC	AGC	AAA	TGT	TGT	AAA	CAT	1320
421	P	T	L	V	E	V	S	R	N	L	G	K	V	G	S	K	C	C	K	H	440
1321	CCT	GAA	GCA	AAA	AGA	ATG	CCC	TGT	GCA	GAA	GAC	TAT	CTA	TCC	GTG	GTC	CTG	AAC	CAG	TTA	1380
441	P	E	A	K	R	M	P	C	A	E	D	Y	L	S	V	V	L	N	Q	L	460
1381	TGT	GTG	TTG	CAT	GAG	AAA	ACG	CCA	GTA	AGT	GAC	AGA	GTC	ACA	AAA	TGC	TGC	ACA	GAG	TCC	1440
461	C	V	L	H	E	K	T	P	V	S	D	R	V	T	K	C	C	T	E	S	480

Figure 15C

1441 TTG GTG AAC AGG CGA CCA TGC TTT TCA GCT CTG GAA GTC GAT GAA ACA TAC GTT CCC AAA 1500
481 L V N R R R P C F S A L E V D E T Y V P K 500

1501 GAG TTT AAT GCT GAA ACA TTC ACC TTC CAT GAT ATA TGC ACA CTT TCT GAG AAG GAG 1560
501 E F N A E T F F T F H A D I C T L S E K E 520

1561 AGA CAA ATC AAG AAA CAA ACT GCA CTT GTT GAG CTT GTG AAA CAC AAG CCC AAG GCA ACA 1620
521 R Q I K K Q T A L V E L V K H K P K A T 540

1621 AAA GAG CAA CTG AAA GCT GTT ATG GAT TTT GCA GCT TTT GTA GAG AAG TGC TGC AAG 1680
541 K E Q L K A A V M D D F A A F V E K C C K 560

1681 GCT GAC GAT AAG GAG ACC TGC TTT GCC GAG GGT AAA AAA CTT GTT GCT GCA AGT CAA 1740
561 A D D K E T C F A E E G K K L V A A S Q 580

1741 GCT GCC TTA GGC TTA TAA CAT CTA CAT TTA AAA GCA TCT CAG 1782
581 A A L G L * 585

Figure 15D